that came up, but just delineate if it has not been approved by CDER--CBER, excuse me--it should not be used for screening.

DR. CHARACHE: Let's take first--let's complete the issue that Dr. Thrupp has raised, and then we'll pick up on this one. Let's vote on--yes, Dr. Thrupp

DR. THRUPP: Concerning the first issue, I would certainly agree with Dr. Reller's comments. On the other hand, I would suggest that we have seen enough data that there is just enough waffle, just enough discrepancies, and especially in certain of the populations tested, that we could make a recommendation that a repeat test, data on just repeating their sera and a confirmatory test be done, and that the carrot might be that it may well be it's a better test than the reference method, but this is the only way they're going to find out, when we're speaking of HBsAG.

DR. CHARACHE: All right. Let's vote on whether we think this should be a condition of--prior to approval at this time. The recommendation is that it be required that there be a double testing plus a confirmatory test for HB surface antigen, for all tests. This time we'll start at the far end. Would you--

DR. SPECTER: I guess I'm against that.

DR. CHARACHE: Dr. Reller?

DR. RELLER: I am--I am for confirmation and

neutralization--I am for--what we're talking about is making sure that this test is specific, and I'm for that.

DR. CHARACHE: Dr. Tuazon?

DR. TUAZON: I guess I can just vote yes or no, right?

DR. CHARACHE: Yes.

DR. TUAZON: Yes. Okay, I would vote yes, but I think I still have problems in terms of the test was really not done in a clinical setting.

DR. CHARACHE: Dr. Sanders?

DR. SANDERS: I would agree that there should be a repeat test.

DR. CHARACHE: Dr. Weinstein?

DR. WEINSTEIN: Well, I'm not sure how to vote, because I agree that there should be a repeat test but I'm not sure I want to add the burden of having the manufacturer develop a second confirmatory--yet another test to confirm the repeat.

DR. CHARACHE: I'm just glad I don't have to vote. Dr. Seeff?

DR. SEEFF: I'm really not smart enough to know what the best thing is to do. I also tend to believe that a repeat test certainly should be done. I can't speak to the issue of a confirmatory test. I would probably not require that, but I would like to see a repeat test.

DR. CHARACHE: Dr. Wilson?

DR. WILSON: I would like to echo that. I would like to see a repeat test, but in the absence of a confirmatory test, I'm not sure what good a repeat test does, because you need a tie-breaker, and since a confirmatory test doesn't exist, I'm not sure how we can vote on that. So I would guess that I'm in favor of the principle.

DR. THRUPP: Could I amend my motion, then? It's a valid consideration that there has not been a confirmatory test, and that's liable to delay things too much, but I would think that a repeat test would be helpful in view of its importance. And so if I could amend the motion to a repeat test, that's--

DR. CHARACHE: Well, I think people have already pretty much voted on this, I think.

DR. SEEFF: Could I again get clarification on this? We are talking about a repeat test on the same sample, not another sample.

DR. THRUPP: Yes, a retest.

DR. CHARACHE: Yes. Okay, I think we have provided guidance on that. So the group has voted that a positive should be repeated prior to reporting, and that there are issues associated with specific populations that have been defined. Is there anything else anyone would like

to add on this particular assay? Dr. Thrupp

DR. THRUPP: That post-marketing, assuming the other conditions are met, that post-marketing the sponsor be requested to provide additional data on high risk populations that have not been studied.

DR. CHARACHE: That has already been voted. Yes, that has already been covered

DR. THRUPP: Okay. I wasn't sure we voted on that specifically.

DR. CHARACHE: Yes. Yes, that's fine. All right. I think at this time we then should be prepared to determine whether we want to approve or disapprove this product with the conditions that we have heard, so we are going to vote on approval. It was put forward as an approval, it was seconded, and we have discussed the conditions.

So can we assume that those conditions are our amendments to the approval, so that we can now vote on the amended motion? So we are now voting on approval with the conditions as voted upon by this panel.

DR. WEINSTEIN: Do you want me to read them off?

DR. CHARACHE: Yes.

DR. WEINSTEIN: Okay. The conditions include, number one, the need for more data on the use of the test in pregnancy; number two, need for sufficient data on patients at high risk for hepatitis B, and I guess other bloodborne

pathogens; number three, the need for more data on patients who meet the current standard definition for chronic hepatitis B infection; and, number four, a repeat test on the same sample to confirm a positive result.

DR. CHARACHE: And these were all voted as pre-markets. Dr. Seeff?

DR. SEEFF: Could I just again for clarification, because I'm also a little elderly and I can't always keep everything in my head, I'm still a little uncertain about the vaccinees, when the samples were obtained. Do we know that the--

DR. CHARACHE: No, that's not included as an indication for this particular one. That's the last. That's the anti-HB, so it's just the first four. Okay?

Mr. Gates? Dr. Gates?

DR. GATES: Yes. I can't vote but just as a point of procedure, I'm trying to follow where we're going here. We're talking about the surface antigen.

DR. CHARACHE: Right.

DR. GATES: We've made a motion to approve it with amendments, and some of those, pre- and post-marketing, we have discussed those, and then we're going to go through the next five along the same route, right?

DR. CHARACHE: Yes.

DR. GATES: Okay.

DR. CHARACHE: So that we now will, we will ask the panel to vote this motion up or down with the amendments that you have heard. This time we'll start with Dr. Thrupp.

DR. THRUPP: Yes.

DR. WILSON: No.

DR. SEEFF: I would vote for approval with conditions, pre-market.

DR. WEINSTEIN: I vote for approval with conditions.

DR. SANDERS: Approval with conditions.

DR. TUAZON: Approval with conditions.

DR. RELLER: The way we've approached this makes it very difficult for me because, you know, I do not think that this product for surface antigen testing should be approved unless all of the conditions were met before approval. And to me that means in the late afternoon on the 20th that it's not an approvable product as presented for any of the indications there, and I think it's safer to say that straight out, with the benefit of all the discussion we have had, for the kinds of things that would be required to make it an approvable. So consequently I vote no.

DR. SPECTER: Approval with conditions.

DR. CHARACHE: Okay. Thank you very much. Now let's go to the--okay, we'll take a five-minute break.

[Recess.]

DR. CHARACHE: We are going to start again, please. Okay. We are going to take up the second issue, which adds the--can we put back the summary of--what was up there before? Who has got the indications? Could we have the indications, please?

When we talk about the hepatitis, anti-hepatitis surface antigen, we are adding the item on the bottom, which is the indication for post-exposure to hepatitis B in potential hepatitis B vaccine recipients, and I can't quite read that at that angle. Somebody--

DR. SANDERS: And to determine the presence of an immune response in vaccine recipients.

DR. CHARACHE: Thank you. And to determine the presence of an immune response in vaccine recipients.

DR. SPECTER: But that's only for anti-HBs.

DR. CHARACHE: That's what we're going to discuss next.

DR. SPECTER: Okay.

DR. CHARACHE: All right? So we need a motion for the anti-HBs, which has the same previous ones plus the one we just read. Dr. Specter?

DR. SPECTER: Well, I don't want to go through the whole other discussion. I would make a motion for approval with conditions.

DR. CHARACHE: Would you list the conditions, and

would you like to have read to you the ones we have already discussed?

DR. SPECTER: Yes. I would simply say that we go with the conditions there and add one, and that's to address that last point. And that is that a panel of vaccinated individuals who have gone through a normal vaccination process and are--I'll say a defined time, and I'll say something like between 3 and 12 months post-vaccination, but better leave it to FDA's discretion, but a panel of that nature be added as an additional condition.

DR. CHARACHE: Could you--we'll ask if someone wishes to second that motion.

DR. THRUPP: Could I add--ask for an amendment to it, or a condition?

DR. CHARACHE: No, no. We need a second first, if we have a second.

DR. SEEFF: I'll second the motion.

DR. CHARACHE: Dr. Seeff seconds the motion. Now I'm going to ask Dr. Weinstein if he would read the specific conditions that were on the table before so that's very clear, what is being voted on.

DR. WEINSTEIN: Okay. The conditions are, one, need for more data on the use of the test in pregnancy; two, obtain sufficient data on patients with high risk for bloodborne pathogens; three, obtain more data on patients

with a standard definition--who meet the standard definition for chronic hepatitis B infection; and, four--I think the fourth one was specific for hepatitis B surface antigen, which was to repeat any positive test on the same sample to confirm the result.

DR. CHARACHE: All right, so do we have a recommendation that that last one be deleted for this? Is that a friendly amendment?

DR. SPECTER: Yes.

DR. CHARACHE: Okay. That has been accepted by the person who made the motion, and is that all right with the person who seconded it? Okay. Dr. Thrupp

DR. THRUPP: One of the--the only real uses, aside from the development of vaccines for anti-HBs, is in health care workers and vaccine recipients who have been vaccinated 5 years, 10 years, whatever, long ago, when the titers, as Dr. Seeff pointed out, are waning and where you're going to get much lower levels. So in addition to the time intervals that Dr. Specter mentioned, I would add a late sample of vaccine from a number of years ago, and I would leave that to the FDA to define the time interval.

DR. CHARACHE: All right. We have a suggestion that we not only have a post, 3 to 21 months post-vaccine, but also a later sample. Can we have a discussion, whether people feel that's a needed addition? Dr. Specter?

DR. SPECTER: It's easy enough to do. I don't see it should be a problem.

DR. CHARACHE: All right. Dr. Specter feels that this would be reasonable.

DR. SEEFF: The assumption is that the test will be done at the time specified or decided upon by the FDA, but also compared to the current reference. Is that the assumption?

DR. CHARACHE: Yes. The assumption is that since that is the criteria that has been used by DiaSorin, that this would be done. Any other discussion of that point?

[No response.]

DR. CHARACHE: All right. Can we have a vote? And this time we'll start again with Dr. Seeff.

DR. SEEFF: I'm going to move in the middle there.

DR. CHARACHE: That's the only place we haven't started.

DR. SEEFF: I vote in favor of that motion, since I seconded it.

DR. CHARACHE: Okay.

DR. WILSON: I am in favor of that motion.

DR. CHARACHE: Dr. Thrupp

DR. THRUPP: In favor.

DR. SPECTER: In favor.

DR. RELLER: All of those additional data and

studies that were delineated, all of that was pre-marketing?

DR. CHARACHE: Yes. All of the previous votes were for pre-market.

DR. RELLER: This is a tactical thing. I mean, I think this is all good. I just--my reservation is that "approvable with conditions" I would have thought is when everything looks good except there's one little niche and that needs to be taken care of, and this is much more comprehensive than that. And I think the discussion of what needs to be done is very important and helpful, but I'm uncomfortable with the ambiguity of approvable with all these conditions versus it's just not approvable at this time, based on the information we have. And consequently, for consistency, I vote no.

DR. CHARACHE: We are voting now not on the approvable with conditions or not, but rather whether an additional condition, should that be approved, be additional information on hepatitis antibody, surface antibody, in patients who have been vaccinated--in subjects who have been vaccinated.

DR. RELLER: Oh, I'm all for that.

DR. CHARACHE: Okay.

DR. TUAZON: I'm in favor.

DR. CHARACHE: Thank you.

DR. SANDERS: I'm in favor.

DR. WEINSTEIN: I'm in favor.

DR. CHARACHE: All right, so it's unanimous that this would be an advantage and should be required if it's approved. Any other conditions that people would like to discuss on this? Dr. Thrupp?

DR. THRUPP: You read off the same conditions that were raised in conjunction with the surface antigen test.

DR. CHARACHE: Yes. Those have all been--are part of the motion.

DR. THRUPP: Right. I wonder if whoever the primary mover was, I guess Dr. Specter, would feel that we really need to request the same extent of data on some of the specialized populations that we asked for with the surface antigen, because in the anti-HBs the test doesn't make that much difference.

DR. CHARACHE: Well, it is also a sign of convalescence when it appears.

DR. THRUPP: Well, okay, but it's not so critical, and there's other ways to look at that too. I'm not sure. I mean, maybe we could ask Dr. Seeff or Dr. Alter if they would feel that they need to redo all the anti-HBs in all these populations that we asked for where we felt that the surface antigen was more critical.

DR. SPECTER: Can I comment, since--

DR. CHARACHE: Yes.

DR. SPECTER: I think one of the valuable things is, if you're going to do the surface antigen and you want data, doing the surface antibody as well is very good confirming data that you have conversion, if in fact you have gone from antigen to antibody

DR. THRUPP: Oh, okay.

DR. SPECTER: And to do that test along with the others, you're not looking at a different population. I really don't think it's adding a burden.

DR. SEEFF: As a clinician, and I'm different from Dr. Alter who may be a regulator, I believe that a patient has not recovered from hepatitis B until I know that they are anti-HBs positive or at least they have lost their surface antigen, because there are some people who retain their surface antigen and there's no symptoms that tell you they retain that, and so I would like to know that people have completely recovered from hepatitis B, and it's just as easy to do anti-HBs.

And of course there is the other issue about whether you should follow up vaccination by determining whether you have anti-HBs, because there are some people who do not respond, and then 10 years later when you don't identify it, you're not sure whether they didn't have it in the first place or--and in which case there is a difference from the person who had it and now has lost it, because

that's now in memory and that will be boosted, that response, when reexposed. So I do personally like to follow up with anti-HBs, as a clinician.

DR. CHARACHE: All right. Are we prepared to vote on the motion that's on the table?

[No response.]

DR. CHARACHE: Hearing no complaints, we will, and we'll start with Dr. Specter.

DR. SPECTER: I'm for the motion.

DR. RELLER: Against.

DR. TUAZON: I'm for the motion.

DR. SANDERS: I'm for the motion.

DR. WEINSTEIN: I'm in favor.

DR. SEEFF: I'm in favor.

DR. WILSON: I'm in favor

DR. THRUPP: In favor.

DR. CHARACHE: Okay. Thank you very much.

The next test we will take up is the anti-hepatitis Be antigen. I mean e antigen. Sorry. Hepatitis Be antigen. Yes?

DR. SPECTER: Since I primarily reviewed this, I would make a motion for approval, and the rationale for that is that in somewhere near 1,000 specimens tested, the high and low populations, the test performed with a very high level of sensitivity and specificity under all conditions.

DR. CHARACHE: We have a motion for approval of the hepatitis Be antigen. Any discussion? Oh, anyone second the motion?

DR. SANDERS: I'll second the motion.

DR. CHARACHE: Dr. Sanders seconds the motion. Discussion?

DR. TUAZON: I have some questions because I didn't see the data on this, I didn't review the data. Was there information in terms of a population that was monitored after HBV therapy in that group with the use of the HBe antigen?

DR. SPECTER: There was not specific information set aside about therapy.

DR. CHARACHE: That is one of the indications for use, is monitoring of therapy. So the question has been raised--yes, Dr. Seeff?

DR. SEEFF: Dr. Specter, when you say that indeed that the test behaved adequately, what do you mean by that? I mean--

DR. SPECTER: There are four groups that were tested.

DR. SEEFF: Right.

DR. SPECTER: Of those four groups, as I said, there were somewhat more than 1,000 specimens and there were, I believe, 4 specimens out of the 1,000 where there

was discordance with the preference test. There were no large groups where there was more than one. The sensitivity at its lowest was 97.8 percent. The specificity at its lowest was 98.5 percent.

DR. SEEFF: I regret that I didn't review this in any great detail. The e antigen was done only when the surface antigen was positive, or also in other groups as well?

DR. SPECTER: I believe it was done on the same bank of specimens, whether positive or negative.

DR. SEEFF: So it was negative always when surface antigen was negative?

DR. SPECTER: In the--as far as I know. I wouldn't state that unequivocally, but if there was discordance like that, it may have happened once in 1,000 specimens. But if you look at the hospitalized patients that did not have hepatitis B or the first time blood donors, there were--there was one positive out of some 800 specimens, and that was consistent with the Abbott test.

DR. CHARACHE: Dr. Thrupp

DR. THRUPP: Dr. Tuazon asked about the treated patients, and I'm not sure I have the right table, but it looks as though there were 15 patients that were treated and followed. That's on page--well, it's in the book. Is that a correct number, so that we would have--there is some

information, if they were--those were followed serially, so that gives more information than just a single test, but--well, it says SSED 12 but it doesn't give the results there.

MS. SMITH: That's the summary of safety and effectiveness.

DR. THRUPP: That's the number of patients studied, right?

MS. SMITH: No, SSED 12 is-

DR. THRUPP: Safety, okay. So that's the denominator that we're talking about in terms of, if this is correct, that were treated. So it's not a large number, but evidently the agreement with the reference test was very good.

Five were treated with no response, five were treated with partial response, and five were treated with sustained response.

DR. TUAZON: Well, the--

DR. CHARACHE: Yes? Dr. Tuazon.

DR. TUAZON: The question I have, is that enough information or enough data to claim it in your labeling for intended use?

DR. CHARACHE: Also, it does not address the other issues that were raised, the use of the test. Now it's an antigen test, it's not an antibody test. It doesn't address the issues of the definition of chronic hepatitis or the

other issues that had been defined as needing more data.

DR. SEEFF: It seems to me that this is a test that's not done in a vacuum. The only reason to go an e antigen, I think, is to determine whether somebody is surface antigen positive, is replicating or nonreplicating, highly infectious or less highly infectious. So the only reason to do it is if the surface antigen is positive. Since we have certain provisos for the surface antigen, that has to be met in order to be able to--for me to be able to approve e antigen, because e antigen on its own doesn't have any meaning in this.

DR. CHARACHE: All right. Now I am just recognizing that we are again out of order. The recommendation was made for approval and seconded, so if it's for approval and seconded, we should not discuss it until we have voted whether we do or don't accept that recommendation. So we will stop discussion at this point and we will vote on whether to approve the hepatitis e antigen, hepatitis Be antigen.

DR. SANDERS: Madam Chair, I'm sorry to interrupt. The indications that are listed on the transparency are not the same indications that are listed in our copies of the intended use--the package insert. What is there is not what we have here.

DR. CHARACHE: All right. Let's be sure that we

are correct on that. All right. This says intended use is for in vitro enzyme immunoassay, intended use in the qualitative determination of hepatitis Be antigen in human serum or plasma, when used in conjunction with other hepatitis B marker assays as appropriate. This assay is indicated for use as an aid in the diagnosis and monitoring of hepatitis B virus, HBV, infection in an adult population, and to monitor hepatitis B therapy.

DR. TUAZON: That's the first three that are listed.

DR. CHARACHE: Yes, that's the first three that are listed there. It's just a listing instead of the precise wording. It does not say in acute and chronic in this case. It says in an adult population.

DR. SANDERS: Right. I just wanted to clarify that.

DR. CHARACHE: Certainly. All right, so let's vote on that indication for use. Where will we start? Would you start?

DR. SPECTER: I am for approval.

DR. CHARACHE: Dr. Reller?

DR. RELLER: Against approval with no conditions attached, which is the definition of approval.

DR. CHARACHE: Dr. Tuazon?

DR. TUAZON: No approval.

DR. SANDERS: Approval.

DR. WEINSTEIN: No approval.

DR. SEEFF: I am also against that without the attachment of conditions.

DR. CHARACHE: Dr. Wilson?

DR. WILSON: Against approval.

DR. CHARACHE: Dr. Thrupp

DR. THRUPP: For approval.

DR. CHARACHE: All right. We have three votes for approval, five votes against approval, so at this point we'll ask for another motion. Dr. Thrupp

DR. THRUPP: Can you entertain a little discussion? Dr. Seeff's concern--

DR. CHARACHE: We can entertain discussion after we have a motion. May we have a motion of either approval with conditions or disapproval?

DR. SEEFF: I would put a motion forward for approval with conditions.

DR. TUAZON: I would second that motion.

DR. CHARACHE: All right, and would you stipulate the conditions? Do you want to hear the ones that we had on the table before?

DR. SEEFF: Well, I would link it directly to hepatitis B surface antigen. If the conditions that we require for approval, full approval of the hepatitis B

surface antigen test is met, I would be willing then and in fact require that HBe antigen testing also be approved in order to support that test.

DR. CHARACHE: Would you, again as a friendly amendment, accept that if it were positive, you did not have to repeat it, or would you want it repeated, which is the requirement of the previous one?

DR. SEEFF: I think that if we have had two positive tests for surface antigen, and e antigen is positive--I am now struggling with this--my initial thought is, if e antigen is positive once only and with strong titer, I would be willing to accept that. I would really--perhaps I would like to hear more discussion from people who may be more knowledgeable about this.

DR. SANDERS: This is a qualitative assay.

DR. SEEFF: You know, if we have complete, if we have absolute assurance that the surface antigen is positive based on the two tests, if that is assurance enough, an e antigen positive test would be fine, one test would be fine.

DR. CHARACHE: All right. Any other discussion? Dr. Thrupp?

DR. THRUPP: I wonder if Dr. Seeff's concern could be handled by a discussion of the labeling of the product with recommendations as to how it should be used, such as in a cascade, rather than sending them back to the drawing

board for more testing. Specifically, shouldn't the directions for use of the e antigen test be a cascade to be run only if the surface antigen is positive, as with the repeat?

DR. SPECTER: Madam Chairman?

DR. SEEFF: Frankly, I see no reason to do an e antigen test on somebody who is surface antigen negative

DR. THRUPP: Right.

DR. SEEFF: You're wasting money and you're wasting time.

DR. THRUPP: That could be said on the package insert.

DR. CHARACHE: But I think we could come back to that question subsequently.

DR. SPECTER: I just wanted to point out, that was specifically why I asked the question earlier of Dr. Alter about recommendations, and there was a very clear statement made then that you wouldn't attach recommendations for use to that, and that's why I would suggest we avoid that.

DR. CHARACHE: Well, that was her personal view, which the panel can advise on as well.

DR. SPECTER: I understand. I was supporting her position.

DR. CHARACHE: We have discussed that since. Any further additions? Dr. Tuazon?

DR. TUAZON: Yes. I would just like more information in terms of data on its use in monitoring HBV therapy.

DR. CHARACHE: So you would like to request additional data on monitoring HBV therapy.

DR. TUAZON: The number of patients, the--

DR. CHARACHE: Okay. Any other discussion of that?

DR. THRUPP: Pre-market or post-market?

DR. TUAZON: Pre-market.

DR. CHARACHE: Okay, so we have a recommendation from Dr. Tuazon that we add an additional condition, which is that there be more data on its use in therapeutic monitoring. Further discussion on that particular point? Dr. Specter?

DR. SPECTER: I would like to ask why you think that will change the competency of that test?

DR. TUAZON: I just don't know how the test work in terms of its efficacy in monitoring patients who have received vaccine therapy, these 11 patients--is it 11 patients?

DR. CHARACHE: Fifteen patients.

DR. SPECTER: Right, but are you suggesting that that--that treated patients would not react normally?

DR. TUAZON: I don't know that.

DR. CHARACHE: Okay. Is there--Dr. Thrupp

DR. THRUPP: Dr. Specter has pointed out that the reproducibility and the performance of the test was excellent, better than some of the others that we have been looking at, and I would wonder whether such data could be a requirement post-marketing rather than pre-marketing for the e, but that's--

DR. CHARACHE: Yes. I think also that Mr. Simms' data showed an excellent correlation between the two assays in the 15 patients who were monitored.

All right, we'll take a vote on this additional recommendation. Should we require additional pre-market studies to document the performance of this test in patients who are undergoing therapy, therapeutic monitoring? Dr. Seeff?

DR. SEEFF: I would be happy to get post-marketing information.

DR. CHARACHE: Dr. Wilson?

DR. WILSON: I agree.

DR. CHARACHE: Dr. Thrupp

DR. THRUPP: Post-marketing.

DR. CHARACHE: Dr. Specter?

DR. SPECTER: I am against.

DR. CHARACHE: Okay. Dr. Reller?

DR. RELLER: If we don't have enough information

in treated patients and we're getting the other things pre-marketing, I think we ought to get this information pre-marketing also.

DR. CHARACHE: Dr. Tuazon?

DR. TUAZON: Same with me.

DR. CHARACHE: Dr. Sanders?

DR. SANDERS: Post-market.

DR. CHARACHE: Dr. Weinstein?

DR. WEINSTEIN: Pre-market.

DR. SEEFF: Could I change my vote also?

DR. CHARACHE: Yes.

DR. SEEFF: I'm sorry. I would like to say pre-marketing.

DR. CHARACHE: All right. We have a consensus that, with one no vote, that there should be more information obtained. We will now ask for a show of hands. Those who want to suggest that this be obtained post-marketing will vote first, and then pre-marketing. All those who feel that this information should be gained post-marketing, please raise your hands?

[A show of hands.}

DR. CHARACHE: Two. All those who would like to see this information pre-marketing?

[A show of hands.]

DR. CHARACHE: Five. Okay, two to five. Now, any

other points that people would like to put on the table before we vote in favor or against this approval with conditions?

[No response.]

DR. CHARACHE: All right. Let's vote for--all those--we'll go around the table again for those in favor or against the approval with the conditions that have been listed. There are two conditions in addition to--well, actually only one in addition to the ones we voted earlier. We approved the concept that the hepatitis e should be approved in association with meeting the conditions for the hepatitis B surface antigen, and that there be more data on the test in the monitoring setting.

So we'll go around. Dr. Thrupp

DR. THRUPP: Approve.

DR. CHARACHE: Dr. Wilson?

DR. WILSON: Approve.

DR. CHARACHE: Dr. Seeff?

DR. SEEFF: Approve.

DR. CHARACHE: Dr. Weinstein?

DR. WEINSTEIN: Approve.

DR. SANDERS: Approve.

DR. TUAZON: In favor.

DR. RELLER: Approvable with the delineated conditions.

DR. SPECTER: Approve.

DR. CHARACHE: So it's unanimous approval, with the conditions that were listed.

The next test is the antibody to hepatitis e antigen. Do we have a motion?

DR. SPECTER: Since the data were quite similar to the e antigen. I would make the motion for approval with the identical conditions to the e antigen.

DR. CHARACHE: The motion has been made that the test be approved with conditions which are identical to the ones just voted on for the e antigen. Do we have a second?

DR. SANDERS: I'll second that.

DR. SEEFF: Second.

DR. CHARACHE: We have two seconds. All right. Any additional discussion?

[No response.]

DR. CHARACHE: All right. We'll vote, this time beginning with Dr. Weinstein.

DR. WEINSTEIN: In favor.

DR. SANDERS: In favor.

DR. TUAZON: In favor.

DR. CHARACHE: Dr. Reller?

DR. RELLER: Approvable with conditions.

DR. SPECTER: For.

DR. CHARACHE: Dr. Seeff?

DR. SEEFF: In favor.

DR. WILSON: In favor

DR. THRUPP: In favor.

DR. CHARACHE: Okay. That is also unanimous.

The next is antibody to hepatitis B core antigen, anti-HBc, and this is the total antigen--total antibody, total antibody to hepatitis B core. Do we have a motion? Come on, you've had cookies, you have some glucose. Let's have somebody who is willing to make a motion about--

DR. SPECTER: In the interest of time, since obviously this is very closely tied to the surface antigen, I would vote for approval with the single condition that it be pending approval of the surface antigen.

DR. CHARACHE: Do we have a second?

DR. SANDERS: I just need some clarification. The surface antigen was approved with conditions, so you mean once the conditions are met for surface antigen, that this would then also be approved?

DR. SPECTER: Yes, with the understanding that the same--it would undergo the same testing, since it would be appropriate to look at this in that context.

DR. CHARACHE: All right. Now, with that, again as a friendly amendment, you would not require double testing?

DR. SPECTER: No.

DR. TUAZON: I have a question. Would you add also the monitoring therapy that also is claimed in their intended use?

DR. SPECTER: There really is very little value in its monitoring of HBV therapy. Once it's positive, it's positive. It's not going to change.

DR. CHARACHE: Would you like to add, then, that it would not be an appropriate indication for this particular test? That that particular indication be deleted?

DR. SPECTER: Probably. I mean, it has no value.

DR. CHARACHE: Okay, so the recommendation has been made that the indication for use that it be used for monitoring the acute and chronic hepatitis infection, it is recommended that that not be included as a recommendation for this particular test.

Does the person who seconded the motion agree with that amendment? Oh, nobody seconded it. I beg your pardon. Nobody seconded.

DR. SANDERS: Well, I would second it, but I would like to just for the record read the intended use.

DR. CHARACHE: All right, let's read the intended use.

DR. SANDERS: Which is, "ETI-AB COREK PLUS is an in vitro enzyme immunoassay intended for use in the

qualitative determination of total antibody to hepatitis B core antigen in human serum or plasma. When used in conjunction with other hepatitis B marker assays, as appropriate, this assay is indicated for use as an aid in the diagnosis," and we have struck a portion of that, so that it is "as an aid in the diagnosis of hepatitis B virus infection in both low and high risk adult populations, and we have struck the monitoring indication.

DR. CHARACHE: Yes, we struck the "monitor HBV therapy," right. Do we have a second for that? You have seconded it?

DR. SANDERS: Yes.

DR. CHARACHE: Okay. Any further discussion? Dr. Reller?

DR. RELLER: So this motion is approvable with all of the earlier conditions, pre-marketing, with an additional deletion or recommended deletion. This would be a change in labeling, even if those conditions were met and it ended up being approved, that monitoring doesn't have any place in the labeling.

DR. CHARACHE: That is what the discussion is about.

DR. SPECTER: And that it would not require double--

DR. CHARACHE: And it would not require double

testing the way the hepatitis B did.

DR. RELLER: Right, because I think the next part of this, intended use in both high and low risk, just to reemphasize that we have not seen those delineated, high and low risk populations.

DR. CHARACHE: Right, but that was covered earlier. Any other discussion? Dr. Seeff?

DR. SEEFF: Could you just repeat which of these has been deleted?

DR. SANDERS: It's not there.

DR. CHARACHE: The monitoring, the use of this test to monitor HBV therapy.

DR. SEEFF: Okay, so it's acceptable as a monitor for acute and chronic--

DR. CHARACHE: No. Just diagnostic. The monitoring was removed from both places.

DR. SEEFF: Both places, monitoring?

DR. CHARACHE: Yes.

DR. SEEFF: Okay.

DR. CHARACHE: The monitoring is out.

DR. SEEFF: Oh, okay.

DR. CHARACHE: Hearing no other discussion, we will call the question. This time we'll start with Dr. Thrupp.

DR. THRUPP: Approvable as stated.

DR. WILSON: I vote approval.

DR. SEEFF: I vote approval.

DR. CHARACHE: Dr. Weinstein?

DR. WEINSTEIN: Approval.

DR. CHARACHE: Dr. Sanders?

DR. SANDERS: Approval.

DR. TUAZON: Approval.

DR. CHARACHE: Dr. Reller?

DR. RELLER: I just want to make it absolutely clear, this is approvable with conditions, right?

DR. CHARACHE: With conditions, yes.

DR. RELLER: It's a big difference.

DR. CHARACHE: No, this is all approvable with the conditions that we have discussed.

DR. RELLER: Fine.

DR. SPECTER: For.

DR. CHARACHE: All right, and the last of these is the core, hepatitis B core IgM. Can we hear a motion on that?

DR. SPECTER: Do you want me to continue? I make a motion for approval with conditions similar to what we just approved for total Ig, but with one additional condition, and that is that there be additional testing with specimens that are validly shown to contain IgM by the preference test so that we know that this test works for the

IgM.

DR. CHARACHE: All right, so we have heard that this is recommended for approval with the same conditions as with the total anti-core, plus additional testing to prove that this test works when there is IgM antibody present. We need a second?

DR. WEINSTEIN: I second.

DR. CHARACHE: Dr. Weinstein seconds that motion. Any further discussion?

DR. RELLER: Steve, do you--did you mean to delineate the effect of storage and handling on the protection of IgM?

DR. SPECTER: Yes, in essence. I mean, we saw that there was a problem with storage, so we need some well defined specimens that we know have IgM in them.

DR. RELLER: And delineate the effect of whether they are, you know, frozen, frozen at what temperature, et cetera. Because this was one of the issues before, is the robustness of the IgM, even if it were present in the first place, depending on how this--for testing and handling of specimens it seems to me that that's a very important issue to be delineated, since as a single sample, as Dr. Seeff pointed out before, we depend a lot on an IgM response to make a diagnosis of acute disease. Correct?

DR. SPECTER: I would simplify it by simply saying

to include the effects of conditions of storage as delineated by the FDA.

DR. CHARACHE: All right, so that you would like to add that the FDA should assist in delineating the conditions of storage prior to testing. Dr. Wilson?

DR. WILSON: Dr. Reller has previously raised the issue of the ambiguity between the term "disapproval" and "approval with conditions," and we're to the point now where this has a lot of conditions on it. But the one that bothers me is the fact that this is a test specifically for IgM, and yet we're saying we need to go back and get better sera with no IgM, retest the issue of the effect of storage, and it seems to me that there is little point in approving a test for IgM when you have serious doubts about whether that test detects IgM or not. So this is one where I think we may have crashed the threshold from approval with conditions into the arena of disapproval.

DR. CHARACHE: Dr. Thrupp

DR. THRUPP: I thought we heard data, perhaps not in detail, that made everybody happy, but there was storage, frozen, thawing data that was discussed or mentioned. Do you want more detail or larger numbers, or--I thought that the data looked good. We didn't explain the clinical lack of IgM in certain populations--

DR. CHARACHE: I think--yes, I think-

DR. THRUPP: --but that means you're asking for more clinical studies, then, prospectively or how, before it's approvable.

DR. RELLER: My concern was that there were a series of specimens that should have had IgM present, that were not there, I think from what was defined as acute hepatitis B, that were surface antigen positive but lacked IgM anti-core. And I am not sure exactly of all the conditions, since I didn't review those.

But I am willing for the FDA to delineate what those specimens should be, but I think it needs to be done, because it wasn't a matter of showing that the test wasn't effective, because the preference test didn't detect the IgM as well. So I don't see that there's a problem with the test; I just want to make sure that enough of the right kinds of specimens are tested

DR. THRUPP: It's going to make a big difference to the sponsor whether you're asking him to go back and test a lot more clinical samples and find cohorts where there's going to a positive IgM, and that's not going to be necessarily too easy.

DR. CHARACHE: Well, it's possible--

DR. THRUPP: As opposed to merely doing more data on storage.

DR. CHARACHE: --it's possible that he may find

another vendor who has better preserved samples or something of that type.

Could we vote now on that requirement, that there be additional data on samples that are known to have anti-IgM in the proportion that they should to be defined as acute hepatitis? Let's vote on that, and then we'll vote on the full recommendation. Would you start this time?

DR. SPECTER: Yes. I'm for.

DR. CHARACHE: Dr. Reller, are you for or against the concept of additional samples to show the IgM?

DR. RELLER: Yes, we need more information that the IgM test works.

DR. CHARACHE: Dr. Tuazon?

DR. TUAZON: Yes.

DR. CHARACHE: Dr. Seeff?

DR. SEEFF: Yes.

DR. THRUPP: Yes.

DR. CHARACHE: All right. Now let's vote on the entire discussion, and this, whether you're willing to vote approval with the conditions we've listed. Dr. Seeff?

DR. SEEFF: Yes.

DR. CHARACHE: Dr. Wilson?

DR. WILSON: Yes.

DR. CHARACHE: Dr. Thrupp

DR. THRUPP: Are we talking about the IgM test?

DR. CHARACHE: Yes.

DR. THRUPP: Yes.

DR. SPECTER: For.

DR. CHARACHE: Dr. Reller?

DR. RELLER: I don't believe what we have is approvable, so no.

DR. CHARACHE: Dr. Tuazon?

DR. TUAZON: Yes.

DR. CHARACHE: And Dr. Weinstein had to leave for the last train.

All right. That completes the voting on these proposals. Is there any further one round of advice that we would like to give before we discuss the reasons for our votes? Dr. Seeff?

DR. SEEFF: The reason for my vote? Anything more?

DR. CHARACHE: Yes. I think Dr. Thrupp had an issue he wanted to raise.

DR. THRUPP: It has been mentioned in discussion today, and I think it should be reemphasized, that for probably 95 percent of the hepatitis testing that is done, there is excessive numbers of tests because what is really needed is the B surface antigen as a primary test and then we can come back to the C antibodies tomorrow.

Therefore, in order to conserve resources and not

be doing excessive testing which most physicians will not know how to interpret or not pay attention to anyway, I think that I would like to suggest that some discussion be given to making a recommendation that the package labeling include suggested guidelines for the laboratory to use as a cascade or an algorithm and which tests should be done under which circumstances, starting with the screen for the surface antigen. With the exception--I mean, the vaccination would be another issue for the antibody, but the general concept that directions for the laboratory, how to advise their physicians and how they should report their testing and which tests to do, should be included in the labeling without getting too specific.

DR. CHARACHE: Any other comments? Dr. Specter? Dr. Reller?

DR. RELLER: Although for all of these we voted approvable, or most of us did, approvable with conditions, I think it's important to--in the way of summary, that there were a lot of conditions. And underlying many of them I think was the--or speaking for myself--is the discomfort of using characterization of specimens as a surrogate for knowing explicitly what the clinical status of the patient was and the kinds of patient populations studied, so that in the end there were many questions that in fact, if we had well characterized patient populations, those who had high

risk, low risk populations and so on, things may have turned out differently. But we didn't have that, and it's not having the clinical component in which to properly position these tests. That's one point.

The second one is, I was, no matter what the performance, very uncomfortable with the suggested labeling for intended use because I think it is too inclusive. It is not--does not give sufficient direction for the appropriate position of the individual test.

And, lastly, the definition of "approvable with conditions" gives some examples about what those conditions might be, such as physician or patient education, labeling changes, or further analysis of existing data. And I think that there, in all of these issues there--it is much more than that, and I'll just leave it at that.

DR. CHARACHE: Dr. Tuazon?

DR. TUAZON: I don't have any other comments.

DR. SANDERS: I have two comments, and one has to do also with the data set that was used. We clearly recognize that DiaSorin was dealing with commercially available panels, that they did not themselves go out and collect this data from patients, nor did their principal investigators at the individual sites, which most of us would have in other circumstances, not necessarily for this diagnostic test, but under conditions where we have control

of knowing all of that information.

So my question really is to the FDA. Before something like this actually gets to us, is there a mechanism whereby you can look at the quality of the data set that is utilized, so that we ultimately do not impose quite as many conditions to the sponsor as we have done in this instance?

DR. GUTMAN: Well, that's--there is, in the process of review, if we are certain--certainly if we are certain that something is just, just hands-off, we'll try not to bring it to the panel. We'll try and think of major deficiency letters. We'll try to not approve it. We'll try to screen for the panel.

In the case of this submission, there were some very fundamental intellectual concepts that were on the table in terms of titrating this right, in terms of understanding what the appropriate data sets. There has been a long history of interaction with industry in terms of trying to get the right target and the right balance. There have been various guidance documents that have been put out, and discussions.

And so actually it was important for us, whatever blemishes or whatever beauty this submission has, was to use this as a test case to try the waters. And you may or may not realize it, but in fact the discussion has been

extremely helpful, I think, to me and to members of the team in terms of understanding what kinds of questions to ask and what kinds of thresholds.

It's--we have a basic issue with the archiving of samples, and what I'm hearing around the table is, it's not an issue with the archiving of samples, it's an issue of what characterization on which those archive samples are floating. Those are two different issues.

So I actually think we probably put you all through, and perhaps the sponsor and the review team through a wild ride, but I'm personally grateful because I think it has been helpful.

DR. SANDERS: And the other thing I would like to address has to do with, again, what we put in, what kind of algorithms we put into the package insert. And it would seem to me that the algorithm for how to use the test is not necessarily something that should come from the clinical laboratory, but that's something that should come from the clinical domain as opposed to the laboratory domain, from the clinical domain, something from either our infectious disease professional organizations or our gastroenterology professional organizations, or even some type of NIH type of consensus statement on the use of laboratory diagnostic tools in hepatitis B diagnosis and monitoring. Is that really the role of this body, is what I'm asking, and in my

mind it isn't, but maybe I'm wrong.

DR. GUTMAN: I don't know the answer to that. We are instructed to provide labeling, and I think most members of our division passionately believe that we would like to label it as well as we can, and to put in performance that will drive good behavior and any kind of insights that will help use tests better, and in some products we have actually made as a requisite of clearance or approval, educational programs to make sure that people understand limitations.

Where we might get into trouble and where we would probably have some soul-searching is how far we go in labeling, if we thought we were starting to encroach on the practice of medicine or trying to establish new standards in medicine, and it's not clear to me exactly here where that boundary is. We sometimes turn to CDC, and sometimes we'll develop an MWR to help clarify things. Sometimes we'll work with companies to develop, as I said, educational programs.

You make your best recommendation. We'll try and figure out how to work with the sponsor and do it.

DR. CHARACHE: Perhaps we can add, since I'm on the Clinical Laboratory Improvement Advisory Committee, or CLIA, that the direction that this is going is to assist the laboratory physician in providing the interpretation that will guide the clinical user, because we know that the average clinician doesn't know how to use hepatitis e versus

c, and that to do that, the laboratory physician needs guidance from the manufacturer as to how to use their product. So it's a very positive event which is approved of and supported by clinicians, when they get interpretive information on the report forms.

So that's the direction it's going, and there is a balance. You don't tell them how to do it. You don't tell them how to interpret it, and which patient populations to run it on.

I think we have to move along now.

DR. SEEFF: Could I make a comment?

DR. CHARACHE: Yes. Dr. Seeff.

DR. SEEFF: AS usual, I thought that what Dr. Reller had to say was thoughtful and I support what he had to say. I think that, like he, my immediate preference would have been not to approve this until we had the information.

But I think in the effort to get the information that may in fact actually exist, that would make it possible for us to approve this, I wanted to--I decided to go through with approval with conditions, and I think I would like to have those conditions met because I still am not certain what I have approved. I am not sure that I know exactly what has been tested, and we needed better samples to be absolutely certain. I mean, after all, as scientists we

keep saying we have to base our decisions on facts, and if we don't have the appropriate facts, we can't make that decision.

With respect to the recommendations, there is no question that physicians haven't a clue. I mean, the usual thing at my old hospital where I used to be was that everyone would order everything, the results would come back, and then they would call the lab technician and say, "What the heck does this mean?" And this is in a hospital where we have a lot of interest in viral hepatitis. So there's no question that there should be some understanding about how to use those.

I'm not sure it's fair to ask the industry to do this. I think--I am on a committee, I chair a committee which happens to consist of the VA and CDC and DOD and a number of organizations. There is a hepatitis C working group, and one of the reasons why this was instituted was to come up with general guidelines that everybody could agree on, so that if CDC came out with guidelines, the DOD should not go off and have their own guidelines about testing, and the VA shouldn't go off and have their own guidelines about testing.

I think we need uniform guidelines, and as I mentioned, there has been an effort to do this by laboratorians. I think that's the term that they use. It

was a very carefully orchestrated event in which people from CDC, from the NIH, from the VA and others were involved, and they came up with a very careful document that was presented at the annual association event, AACC, and it was given an opportunity for people to respond to this. And once that was responded to, a document was prepared and that was given to the American Association for the Study of Liver Disease to get their approval as guidelines.

And so a set of guidelines have been formulated, and I think that they need to be formulated by people who are true experts in this. I'm not sure that all of us on this panel are, with all due respect, are necessarily experts to be able to decide what we should be doing at this point. I think we need a group of people to do that, and that in some way has been done.

Perhaps we can speak to CDC, to see if there is another way that that might be considered, but I would certainly think it's a little unfair to ask the companies to say what you should do with the tests. Certainly what they mean I think is important, but not what test to use. That should be done by an expert panel.

DR. CHARACHE: All right. I'm going to interrupt the discussion at this time to say that we certainly hope the sponsors have received some assistance and positive guidance, and have found the deliberations to be of value to

them as well as to the FDA.

We have received information that the weather outside is extremely bad and that the parking lot is very icy. We are going to postpone the open committee discussion that was to begin at 5 o'clock, and will try to fit it in at the end of tomorrow's meeting.

We would like to ask Barbara Weiben, who had requested permission to speak at the open public hearing, if she wishes to present.

MS. WEIBEN: Yes, I do.

DR. CHARACHE: Okay. Come ahead. You're on. If you wish to present, you should present now.

Are you ready? Would you like to discuss for us what the issue is while we--

MS. WEIBEN: I asked for this time in order to present information to the committee about commercially available panels for evaluation of the safety and efficacy of diagnostic test kits. Some of these are products that were used by DiaSorin and other manufacturers in the licensure of existing products and of products that are being presented here, so I thought it would be useful for the committee to see the type of information that we provide with that product and be able to make an assessment of whether or not they're useful or not.

I should mention that the package that Ms. Poole

gave to you includes a summary of my presentation and examples of the product data that is provided with these products.

DR. CHARACHE: Let me also officially introduce you to the group. This is Ms. Barbara Weiben, who is Director of Product Development, Boston Biomedica, West Bridgewater, Massachusetts.

If you wish to begin, you may.

MS. WEIBEN: All right, I can do that. The first type of product that I want to describe for you is what we call seroconversion panels. These are sequential specimens collected from a single person during plasma donation at an FDA-licensed facility, and these donations are made during a period of transition from negative to positive for a particular HBV marker such as HBsAG.

The typical data provided include results for FDA-approved kits and also some research methods such as HBV DNA. We also include data from kits available in the international marketplace. Data from other markers for HBV infection, the six discussed here, are available for the specimens but may be negative, depending on the stage of infection.

I have an example of a condensed version of our data sheet that shows you a fairly common seroconversion panel. The one that I have for you is a 16-member panel, so

we have numbered the specimens from 1 to 16, and we provide the bleed dates for each specimen, and then we number them numerically so it's easy to calculate the interval between specimens. And this particular series would show you that the HBV DNA is positive at specimen No. 4; it would show you data for surface antigen for three typical kits, which are then positive on the next specimen, No. 5. We can skip through the third slide.

Here I have shaded the reactive specimens so it's easier to see, and the DNA here is actually positive in No. 9, and then the HBsAG results are shown for three kits: positive on No. 10, which is 11 days after DNA; and then the two columns on the right show HBe antigen test results which are positive then in specimen No. 15, which in this case is 22 days later than the HBsAG.

Next slide shows a less common type of panel in the marketplace. You won't be able to see the data but it's shaded for you, and this is a 32-specimen series collected over nine months and illustrates transition from negative to positive for all of the markers that you are discussing today. The DNA is positive here in specimen No. 4; followed by surface antigen which is first positive in specimen No. 7; then e antigen which is positive 12 days later; and then core M, which is positive in this series 30 days after the e antigen and is positive at the same time as core total; and

then anti-HBe is positive in the last three specimens, and anti-HBs is positive in the last four specimens. Next slide.

We think that these panels offer certain advantages, in that they are available worldwide to all laboratories. That includes manufacturers, FDA, WHO, or other scientists. And the volumes are sufficient for multiple purposes, such as assay development, ongoing QC, comparison studies, and they provide a benchmark for improvements in technology as years pass. They include pre-infection specimens and the intervals between specimens are short, probably much shorter than would be between clinic visits. Next slide.

Another type of product that we provide are what we call performance panels, which consist of 15 to 25 single specimens from different individuals. These are selected to provide a wide range of reactivity, negative, low and high, and are selected to represent different stages of infection. We provide comparative data for test kits similar to that on the seroconversion panels, and these panels often include later markers such as anti-core, anti-HBs and anti-HBe, which are not always in the seroconversion panels because the series are not long enough. Next slide.

These commercial specimens are collected from plasma donors at FDA-licensed facilities. A medical history

is obtained at the time of donation, and plasma is not collected if the donor is acknowledging symptoms or risk factors for HBV. We can collect plasma if the facility has a special FDA license that is required for collection of HBsAG positive donors. These specimens are naturally occurring. There is no dilution. There is no processing such as defibrination, and there is no preservative added. They are stored frozen.

In conclusion I would like to say since the late 1980s panels of this type have been used worldwide by manufacturers to provide data to regulatory agencies for kit approval, and we ask the panel to consider these products as an acceptable option for use by CDRH in establishing the safety and efficacy of diagnostic test kits.

Thank you.

DR. CHARACHE: Thank you.

Questions of Ms. Weiben?

[No response.]

DR. CHARACHE: I wonder if I could ask what temperature they are stored at?

MS. WEIBEN: These products are stored frozen. And I wasn't intending to comment on this, but I heard a lot of the discussion about core M and--

DR. CHARACHE: No, I'm just wondering if it's frozen at minus 20, minus 70--

MS. WEIBEN: We store them at minus 20, and some of our products which are used for RNA detection for HIV and HCV are now stored at minus 70 in order to maintain the stability of the RNA. But we have observed no loss of the serological analytes when we store the products at minus 20.

DR. CHARACHE: You were going to add something about--

MS. WEIBEN: I was going to comment, and I hadn't intended to do this, about the core M discussion. As a manufacturer of product that includes core IgM, we have done stability studies to look at the stability of that analyte when it's frozen and thawed, and we have real time data and also accelerated stress data to indicate that core IgM reactivity is not lost during frozen storage.

And the other comment I would make related to the specimens that are core M negative, and as part of their presentation is--there is sort of an artificial situation here when you're testing for core M, because the core total assays are designed to be used with a specimen that is undiluted and that detects both IgM and IgG, but the core M assays are designed to be used with a specimen that's diluted 1 to 1,000 or 1 to 2,000. And the reason the assays were designed this way was so that they could be used to identify acute infection, because a more sensitive test with a lower dilution would in fact detect core M much longer,

including people who would be considered chronically infected.

So there is a little bit of an artificial situation there. So, that being the case, you could conceive of a situation where the core total test could be detecting IgM because it's tested undiluted, where the core M assay would not be detecting it because it's a 1 to 1,000 dilution. This might occur early in infection where the titer is rising. And so I just offer that as information for the committee.

DR. CHARACHE: Thank you very much.

We will adjourn for today and reconvene tomorrow at 8 o'clock.

[Whereupon, at 6:18 p.m., the panel adjourned, to reconvene at 8 a.m. on Friday, January 21, 2000.]

CERTIFICATE

I, **ELIZABETH L. WASSERMAN**, the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

Elizabeth L. Wasserman

ELIZABETH L. WASSERMAN